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Successful rehabilitation of female service members suffering traumatic injuries to the maxillofacial region is both a physiologic and psychologic issue. A clinical evaluation to determine if an association exists between sex hormone levels and dental implant success was undertaken. Endosseous dental implants were placed in 3 patient groups: (1) male control, (2) female high estrogen, (3) female low estrogen. Groups were based on ovulation cycles. Serum estrogen (ng/dL), serum progesterone (ng/dL), and serum interleukin-6 (pg/ml) were determined at time of implant placement. Pre- and post-surgical photographs and vinyl-polysiloxane impressions were taken to evaluate crestal alveolar bone loss. Upon data analysis, the authors concluded that the balance of alveolar osseous wound healing was not influenced by temporal fluctuations in the ovulatory cycle.

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Michael F. Cuccinelli LTC DE 17 OCT 96

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The Effects of Estrogen and Progesterone Levels on Osseointegration of Dental Implants

Primary Investigator - LTC Michael F. Cuenin

Table of Contents:

Estrogenic Hormones and Dental Implant Therapy: The Effects of Estrogen and Progesterone Levels on Osseointegration of Dental Implants

Introduction

Osteolytic cytokines are expressed throughout the menstrual cycle, but levels of interleukin-1B (IL-1B), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-a) are highest before ovulation when the levels of estrogen and progesterone are low (1). This temporal fluctuation could effect the early events of alveolar osseous wound healing.

Estrogenic hormones are formed by the ovary, placenta, testes and the adrenal cortex. The major secreted estrogen is 17 B-estradiol which occurs in an equilibrium in the systemic circulation with estrone. A deficiency in these hormones has been linked to osteoporosis. The inhibitory effect of estrogens on bone resorption has been studied both in vitro and in vivo. Despite the debate over the risks versus benefits of hormone replacement therapy, supplemental estrogen has been shown to decrease vertebral and hip fractures in postmenopausal women. Estrogenic hormones therefore inhibit bone resorption in the balance of bone mass regulation (2). The cellular mechanism of this estrogen regulatory role is under investigation (3).

Cytokines are multi functional proteins that are regulatory in nature. Interleukin-6 (IL-6) is a specific 26-kD cytokine produced by a wide variety of cells. IL-6 has been shown to stimulate osteoclasts and bone resorption in vitro. Research has implicated the inhibitory effect of estrogen on IL-6 production with the inhibition of osteoclast activity. Therefore one mechanism of upregulation of osteoclastogenesis due to loss of estrogen could be through increased IL-6 activity (4,5,6). However, recent studies provide evidence of an estrogen receptor on the osteoclast indicating that estrogen may have a direct regulatory effect free of IL-6 influence (7,8).

The metabolic effect of estrogen on bone tissue is of concern in the placement of endosseous dental implants. Bone quality is an optimal concern during the diagnostic, surgical, and restorative phases of implant therapy (9). Longitudinal studies have shown the success rate of single tooth endosseous dental implants to be 91.5% in the anterior region and 94.3% in the posterior region (10,11). We questioned whether endogenous estrogenic hormone levels would effect the rate of clinically successful dental implant integration.

Successful rehabilitation of female service members suffering traumatic injuries to the maxillofacial region is both a physiologic and psychologic issue. A clinical evaluation to determine if an association exists between sex hormone levels and dental implant success was undertaken. The project was performed under the auspices of the Defense Women's Health Research Program.

Methods

Thirty patients were recruited from the patient population of the United States Army Dental Activity, Fort Gordon, Georgia. Patients had been treatment planned to receive at least one endosseous dental implant by the Dental Activity Implant Treatment Planning Board. Patients were informed of the nature of the study and upon their consent a volunteer affidavit was completed. Three patient categories (groups) were established. Group 1 (control) included 10 male volunteers. Group 2 (high endogenous serum estrogens) and group 3 (low endogenous serum estrogens) each included 10 female volunteers. Endosseous dental implant surgery was performed in the usual manner utilizing the Branemark protocol (9). Group 2 patients (high endogenous serum estrogens) had implant placement surgery 10 days after the cessation of their last menstruation. Group 3 patients (low endogenous serum estrogens) had implant placement surgery during their menstruation.

The day of implant placement (phase I surgery) intravenous blood was drawn to determine serum levels of estrogen (ng/dL), progesterone (ng/dL), and Interleukin-6 (pg/ml). After the placement of the cover screw and prior to suturing, a thixotropic vinyl-polysiloxane impression (Blu-Mouse, PARKELL Bio-Materials Division, Farmingdale, NY 11735) of the alveolar crest and implant was made. Additionally, an occlusal photograph of the completed implant with cover screw in place was taken. At the time of implant uncovering (phase II surgery) a second impression was made and a second photograph was taken.

Data analysis would include comparison of the phase 1 surgery (implant placement) and phase II surgery (implant uncovering) impressions and clinical photographs to quantify crestal bone loss. Crestal bone loss and/or failure of any fixture to integrate would in turn be considered with respect to patient serum estrogen, progesterone, and Interleukin-6 levels.

Results

One of the thirty fixtures placed failed and necessitated re-treatment. This is a 97% overall success rate for the surgery. This exceeds recent reports for the favorable outcome of endosseous dental implant placement in a clinical training center (12). All remaining fixtures were uncovered and restored as originally treatment planned.

Two investigators independently analyzed the stone casts made from impressions taken at the time of placement and uncovering. No difference could be noted in any samples excepting that of the failed fixture previously noted. Clinical photographs verified this absence of crestal alveolar bone loss.

The laboratory data by group is seen in the following table:

Group/Lab Value	Estrogen mg/dL	Progesterone mg/dL	Interleukin-6 pg/ml
Group 1 (control)	7.68 ± 2.48	29.77 ± 32.57	$1.52 \pm .48$
Group 2 (high)	14.91 ± 9.92	339.55 ± 63.57	$1.62 \pm .13$
Group 3 (low)	11.10 ± 7.04	143.90 ± 135.06	$1.47 \pm .52$

Analysis of laboratory data showed the following trends. The mean serum estrogen, serum progesterone, and serum interleukin-6 lovels were all higher in group 2 (high endogenous estrogen group). A one way ANOVA showed the p values to be $p=0.0543$ for serum estrogen, $p=0.0346$ for serum progesterone, and $p=0.6925$ for serum interleukin-6. Therfore, only serum progesterone levels were significantly different as a function of the group at <0.05 confidence level. A Tukey-HSD test with a significance level 0.05 showed group 1 (control) to be significantly different from group 2 (high endogenous estrogen) alone.

Discussion

The acceptable clinical success of endosseous dental implants regardless of temporal physiologic fluctuations in the ovulatory cycle was seen. No difference in the clinical healing of the alveolar bone surrounding the implants placed was observed within the confines of this study. Laboratory values studied varied greatly by individual. This wide range of the mean laboratory values within each group may have been corrected by increasing the number of patients in each group. It is obvious however, that the temporal hormonal fluctuation is not the sole somatic control mechanism involved in the complex process of bone metabolism and bone healing. Though estrogen, progesterone, and interleukin-6 effect the cellular activity of osteoblasts and osteoclasts, the complex collaboration of these cells is not solely regulated by these substances.

Summary

The balance of alveolar osseous wound healing was not influenced by temporal fluctuations in the ovulatory cycle. Successful oral rehabilitation of females with endosseous dental implants is not effected by the ovulatory cycle.

Bibliography

1. Vinatier D, Lefebvre-Maunoury C, Bernardi C: The ovaries, the immune system, cytokines: physiology. J Gynecol Obstet Biol Reprod 1993: 22:581-91.

2. Stein JH (editor): Internal Medicine, Ed 4, pp 1350-2, 1518-9. St. Louis, Mosby, 1994.

3. Manolagas SC, Bellido T, Jilka RL: Sex steroids, cytokines and the bone marrow: new concepts on the pathogenesis of osteoporosis. Ciba Foundation Symposium 1995: 191:187-96.

4. Ershler, WB: Interleukin-6: A Cytokine for Gerontologists. J Am Geriatr Soc 1993: 41:176-81.

5. Manolagas SC: Role of cytokines in bone resorption. Bone 1995: 17:63S-7S.

6. Bismar H, Diel I, Ziegler R, Pfeilschefter J: Increased cytokine secretion by human bone marrow cells after menopause or discontinuation of estrogen replacement. J Clin Endocrinol Metab 1995: 80:3351-5.

7. Bellido T, Girasole G, Passeri G et al: Demonstration of estrogen and vitamin D receptors in bone marrow-derived stromal cells: Up-regulation of the estrogen receptor by 1,25-dihydroxyvitamin-D3. Endocrinology. 1993: 133:553-62.

8. Mano H, Yuasa T, Kameda T, et al: Mammalian mature osteoclasts as estrogen target cells. Biochem Biophys Res Commun 1995: 223:637-42.

9. Branemark PI, Zarb GA, Albrektsson T (editors): Tissue-Integrated Prostheses - Osseointegration in Clinical Dentistry, pp 199-209. Chicago, Quintessence, 1986.

10. Zarb GA, Schmitt A: The longitudinal clinical effectiveness of osseointegrated dental implants in anterior partially edentulous patients. Int J Prosthodont 1993: 6:180-8.

11. Zarb GA, Schmitt A: The longitudinal clinical effectiveness of osteointegrated dental implants in posterior partially edentulous patients. Int J Prosthodont 1993: 6:189-96.

12. Minsk L, Polson AM, Weisgold A, et al: Outcome Failures of Endosseous Implants from a Clinical Training Center. Compendium 1996: 17(9):848-859.